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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 7/16, 47/10, 47/42</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/01155</b> <b>(43) International Publication Date:</b> 12 January 1995 (12.01.95)
<b>(21) International Application Number:</b> PCT/EP94/02132 <b>(22) International Filing Date:</b> 29 June 1994 (29.06.94) <b>(30) Priority Data:</b> 93305153.4 1 July 1993 (01.07.93) EP (34) <i>Countries for which the regional or international application was filed:</i> GB et al. <b>(71) Applicant (for AU BB CA GB IE LK MN MW NZ SD only):</b> UNILEVER PLC [GB/GB]; Unilever House, Blackfriars, London EC4 4BQ (GB). <b>(71) Applicant (for all designated States except AU BB CA GB IE LK MN MW NZ SD US):</b> UNILEVER N.V. [NL/NL]; Weena 455, NL-3013 AL Rotterdam (NL). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BEGGS, Thomas, Stewart [GB/GB]; Willowdene, Church Road, Colmworth, Bedford MK44 2JX (GB). HAMMOND, Kevin [GB/GB]; Alderside, 1 Porto Hey Road, Irby, Wirral L61 2XA (GB). KLUGK-IST, Jan [NL/NL]; Baarhoeve 78, NL-3137 RL Vlaardingen (NL).		<b>(74) Common Representative:</b> UNILEVER N.V.; Patent Division, P.O. Box 137, NL-3130 AC Vlaardingen (NL).  <b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> ORAL COMPOSITIONS  <b>(57) Abstract</b>  The present invention relates to an oral care composition comprising an antibody and a surfactant. According to the invention, the surfactant is a nonionic surfactant, which provides for improved compatibility with the antibody and enhances its immunoreactivity on storage and its antibody binding and/or enzyme activity. Specific nonionic surfactants are particular ethylene oxide/propylene oxide block copolymers and ethoxylated hydrogenated castor oil.		

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"Oral Compositions"

5 The present invention relates to oral compositions which  
comprise antibodies.

More particularly, the present invention relates to oral  
compositions which comprise antibodies, the shelf life of  
10 which is improved by the inclusion in the oral composition  
of a certain class of surfactants.

Oral compositions in the context of the present invention  
are compositions for the care of the human teeth and mouth,  
15 and comprise compositions such as dentifrices,  
toothpastes, gels, mouthwashes, powders, tablets, lozenges,  
gargle solutions and the like.

Antibodies in the context of the present invention include  
20 polyclonal antibodies, monoclonal antibodies, antibody  
fragments binding to immobilised antigens, as well as  
antibody or antibody fragment-containing systems as  
described in our EP-A-450,800, 451,972 and 453,097.

25 Oral care compositions frequently contain a surfactant, and  
the most common class of surfactants used in oral care  
compositions is the class of anionic surfactants. The most  
frequently used surfactant of this class is sodium  
laurylsulphate. However, we have found that this surfactant  
30 is rather incompatible with antibodies because it impairs  
their efficacy and shelf-life in the compositions.

We have now found that this disadvantage can be overcome to  
a significant extent by using a nonionic surfactant instead  
35 of an anionic surfactant. We have found that this class of  
nonionic surfactants combines good compatibility with the  
antibodies, providing improved immunoreactivity on longer

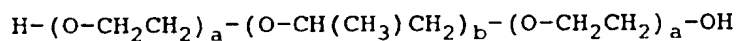
term storage and enhancing antibody binding and/or enzyme activity.

Consequently, in its broadest aspect the present invention  
5 relates to an oral care composition which comprises an antibody and a surfactant, and is characterised in that the surfactant is or comprises a nonionic surfactant.

The invention also relates to the use of a nonionic  
10 surfactant as stabilizing agent in antibody-containing oral care compositions.

An essential element of the present invention is the  
présence in the composition of a nonionic surfactant. The  
15 nonionic surfactant is basically a condensation product of alkylene oxides with a hydrophobic moiety which can be a fatty alcohol, a fatty acid, fatty acid amide, a fatty acid ester, an alkylphenol and so on.

20 Typical examples are the condensation products of ethylene oxide, propylene oxide, butylene oxide and mixtures thereof with C<sub>8</sub>-C<sub>18</sub> primary or secondary, branched or straight-chain alcohols, C<sub>8</sub>-C<sub>18</sub> fatty acid amides, C<sub>9</sub>-C<sub>18</sub> alkylphenols, and block copolymers of ethyleneoxide and  
25 propyleneoxide. Further suitable examples can be found in M. Schick, "Nonionic Surfactants" 1967. Naturally, the nonionic surfactant should be suitable for use in oral products, and should meet the safety requirements for such use. Particularly suitable examples are the ethylene  
30 oxide/propylene oxide block copolymers of the general formula



35 in which a and b are integers greater than 0 which are commercially available from ICI under the trade name "Synperonic PE" or "Pluronic". Of these block

copolymers particularly those, containing 80% by weight of ethylene oxide in the molecule are preferred. Such products have an approximate molecular weight ranging from abt.

4,000 to abt. 15,000, and have an HLB ranging from 27-30.5.

- 5 Specific examples of these preferred products are Synperonic PE/F38, PE/F68, PE/F88 and PE/F108.

Another type of preferred nonionic surfactants is the class of alkoxylated fatty acid esters such as hydrogenated

- 10 castor oil, condensed with ethylene oxide, e.g.

hydrogenated castor oil, condensed with 40 or 60 moles of ethylene oxide, commercially available from BASF under the trade name Cremophor RH40 and RH60. Other suitable examples of nonionic surfactants include polyoxyethylene sorbitan  
15 monolaurate and polyoxyethylene sorbitan monooleate, known as Tween 20 and Tween 80, available from ICI. Mixtures of various nonionic surfactants may also be used.

The nonionic surfactant is used in the present invention in  
20 an amount of 0.01-6%, usually 0.1-3% and preferably 0.25-2% by weight.

Examples of antibodies which are used in the present invention include antibodies against S.sanguis or against  
25 glucose oxidase or against a peroxidase enzyme such as horse radish peroxidase, or against glucosyltransferase; antibody fragments e.g. against lysozyme or against S.sanguis or against a protease. Furthermore, assembly and target bound conjugated complexes (DACC) and self  
30 assembling complexes (DESC) as described in our EP-A-450,800, 451,972 and 453,097 may be used.

- The antibodies are used in the present invention in a therapeutically effective amount. This may vary depending  
35 upon their therapeutic effect and their purity, and in general ranges from 0.01 microgramme per gramme of the composition to 100 milligramme per gramme of the

composition. Usually, the amount will be between 0.3 microgramme to 10 milligramme, and for most practical purposes from 10 microgramme to 1 milligramme. Naturally, mixtures of various antibodies may also be used.

5

The oral care compositions of the present invention may furthermore comprise optional, conventional ingredients such as pharmaceutically acceptable carriers like starch, sucrose, water or water/alcohol systems etc.. Small amounts

10 of surfactants which are compatible with the nonionic surfactants may also be included, such as amphoteric and cationic surfactants. When formulated into a dentifrice, such formulation may contain all the usual dentifrice ingredients. Thus, they may comprise particulate abrasive  
15 materials such as silicas, aluminas, calcium carbonates, dicalciumphosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates and so on, usually in amounts between 5 and 60% by weight.

20 Furthermore, the dentifrice formulations may comprise humectants such as glycerol, sorbitol, propyleneglycol, xylitol, lactitol and so on.

Binders and thickeners such as sodium carboxymethyl-  
25 cellulose, xanthan gum, gum arabic etc. may also be included, as well as synthetic polymers such as polyacrylates and carboxyvinyl polymers such as Carbopol®.

Flavours such as peppermint and spearmint oils may also be  
30 included, as well as preservatives, opacifying agents, colouring agents, pH-adjusting agents, sweetening agents and so on.

Anti-bacterial agents may also be included such as  
35 Triclosan, chlorhexidine, copper-, zinc- and stannous salts such as zinc citrate, sodium zinc citrate and stannous pyrophosphate, sanguinarine extract, metronidazole. Further

examples of anti-bacterial agents are quaternary ammonium compounds such as cetylpyridinium chloride; bis-guanides such as chlorhexidine digluconate, hexetidine, octenidine, alexidine; halogenated bisphenolic compounds such as 2,2'-methylenebis-(4-chloro-6-bromophenol).

Polymeric compounds which can enhance the delivery of active ingredients such as anti-bacterial agents can also be included. Examples of such polymers are copolymers of polyvinylmethylether with maleic anhydride and other similar delivery enhancing polymers, e.g. those described in DE-A-3,942,643 (Colgate)

Furthermore anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin, indomethacin etc. may also be included.

Anti-carries agents such as sodium- and stannous fluoride, aminefluorides, monosodiumfluorophosphate, casein, plaque buffers such as urea, calcium lactate, calcium glycerophosphate, strontium polyacrylates may also be included. Other optional ingredients include vitamins such as Vitamin C, plant extracts, potassium salts such as potassium citrate, potassium chloride, potassium sulphate, potassium tartrate and potassium nitrate.

Buffers and salts to buffer the pH and ionic strength of the compositions may also be included. Liposomes and other encapsulates may also be used to improve delivery or stability.

Furthermore, the oral compositions may comprise anti-calculus agents such as alkalimetalpyrophosphates, hypophosphite-containing polymers, organic phosphonates, phosphocitrates etc..

Other optional ingredients that may be included are e.g.

bleaching agents such as peroxy compounds e.g. potassiumperoxydiphosphate, effervescing systems such as sodiumbicarbonate/citric acid systems, colour change systems, and so on.

5

Other optional ingredients are bacteriophages, enzymes, bioactive peptides and anti-bacterial adhesion polymers.

When formulated as a mouthwash, the oral care composition  
10 usually comprises a water/alcohol solution, flavour, humectant, sweetener and colorant.

The present invention will further be illustrated by way of Example.

15

#### EXAMPLE 1

20

The effect of Synperonic PE/F68 and Cremophor RH40 on the binding of a polyclonal antibody to its antigen was examined using the standard enzyme immuno assay system shown below:

25

See fig. 1

30 To a washed suspension of S.sanguis cells was added anti-S.sanguis bovine hyper-immune serum (1/100 final dilution in phosphate buffered saline (PBS)). Following 30 minutes incubation at approximately 20°C, any remaining unbound anti-S.sanguis antibody was removed by centrifugation of  
35 S.sanguis cells, followed by resuspension in PBS, repeated three times. Commercial anti-bovine horse radish peroxidase (HRP) conjugate (Zymed) and anti-bovine glucose oxidase



(GOx) conjugate (Cappel) were added simultaneously to suspended target cells (both at a final dilution of 1/100 in PBS), with incubation and subsequent wash steps as before. The presence of bound GOx and HRP on the bacterial cell surface was then detected using enzyme substrate containing glucose and tetramethylbenzidine; the combined activity of GOx and HRP resulting in formation of a blue product measurable by spectrophotometry. A control preparation was included in which the first antibody (anti-S.sanguis) was omitted, to confirm that subsequent enzyme-immunoconjugate binding was specific.

A number of S.sanguis cell suspension enzyme immunoassays were performed in which varying concentrations of nonionic surfactant (in the range 0.05%-10% w/v) were added to antibody containing solutions and wash solutions, before mixing with target S.sanguis cells. The effect of the nonionic surfactant at each concentration upon the levels of bound GOx and HRP activity, and consequently upon the efficiency of antibody/antigen binding interactions at each stage of the assay was measured as a function of product formation (OD<sub>450</sub>).

Nonionic-surfactant concentrations of up to 10% w/v did not interfere with antibody/antigen interactions as measured in this immunoassay system. Nonionic-surfactant concentrations in the range 0.001%-10% w/v appeared to significantly enhance the enzyme activity measured.

The nonionic surfactants tested were Synperonic PE/F68 and Cremophor RH40. For comparison an anionic surfactant, sodium dodecylsulphate was also tested.

	Detergent Concentration % (w/v)	O.D. 450 nm		
		Synperonic	Cremophor	SDS
5	10	1.928	1.212	0.006
	5	1.974	1.132	0.004
	2	1.609	1.097	0.009
	1	1.484	1.014	0.026
	0.5	1.306	0.944	0.021
10	0.2	1.162	1.049	0.049
	0.1	1.122	0.821	0.132
	0.06	1.013		
	0.05		0.938	0.162
	0.015	0.84		
15	0.001		0.835	0.84

**EXAMPLE 2**

20

A second enzyme immunocomplex was used to investigate the effect of Synperonic PE/F68 and Cremphore RH40 upon monoclonal antibodies. The integrity of the complex below depends upon a greater number of antibody/antigen

25 interactions than that of Example 1. Both anti-enzyme antibodies are murine monoclonals.

See fig. 2

30

Reagents were added in two steps, as in the previous example, with initial exposure of S.sanguis cells in suspension to the primary polyclonal mouse anti-S.sanguis antibody (1/100 final dilution), followed by simultaneous  
35 exposure to the remaining reagents. The two incubation

steps were interspersed with buffer washes and followed by substrate addition as described in Example 1.

Nonionic surfactant concentrations up to 10% w/v did not interfere with antibody/antigen interactions as measured in this immunoassay system.

Detergent Concentration % (w/v)	O.D. 450 nm		
	Synperonic	Cremophor	SDS
10	1.01	0.888	0.002
5	0.832	1.323	0
2	0.789	1.032	0
1	0.806	0.911	0
0.5	0.827	0.683	0
0.2	0.704	1.136	0
0.1	0.644	0.507	0.159
0.05	0.659	0.659	0.985
0.001	1.16	1.163	1.165

### EXAMPLE 3

The effect of Cremophor RH40 and Synperonic PE/F68 upon binding of anti-lysozyme Fv immunoglobulin fragment (prepared by genetic engineering techniques) to lysozyme was investigated using the standard assay system shown below:

See fig. 3

Anti-lysozyme Fv fragment, rabbit anti-mouse Fv and commercial goat anti-rabbit alkaline phosphatase conjugate

- were added sequentially to lysozyme immobilized on the surface of a nylon peg. In each case 60 minute incubations at 37°C were followed by buffer washes to remove unbound reagents. Finally para-nitrophenolphosphate enzyme
- 5 substrate solution was added and generation of the yellow product was measured by spectrophotometry ( $OD_{405}$ ). No adverse effect upon fragment binding was observed at a nonionic surfactant concentration up to 10% w/v.
- 10 Nonionic surfactant concentrations in the range of 0.02%-10% w/v appeared to significantly enhance the enzyme activity measured.

Detergent Concentration % (w/v)	O.D. 450 nm		
	Cremophor	Synperonic	SDS
10	0.826	1.05	0.047
5	0.834	0.981	0.048
2	0.82	0.903	0.052
1	0.823	0.881	0.062
0.5	0.787	0.92	0.073
0.2	0.787	0.929	0.375
0.1	0.76	0.965	0.627
0.05	0.778	0.924	0.635
0.02	0.764	0.894	0.603
0.001	0.642	0.641	0.642

#### EXAMPLE 4

The standard assay format shown below has been developed to evaluate the resistance of an immunoglobulin, pre-bound to the corresponding antigen, to surfactant induced denaturation or deformation. The relative resistance of polyclonal and monoclonal mouse anti-S.sanguis antibodies were measured.

See fig. 4

Antibody reagents were added sequentially to whole S.sanguis cells immobilized on plastic microtitre dishes, with intermediate wash steps to remove unbound antibody. Varying concentrations of nonionic surfactant or sodium dodecyl sulphate (SDS) were added to wells containing bound anti-S.sanguis antibody and incubated for 20 minutes at approximately 20°C. After further washing, anti-mouse immunoglobulin-alkaline phosphatase conjugate was added to

detect bound antibody.

Nonionic surfactants at concentrations up to 1% (w/v) did not reverse the binding of murine monoclonal antibodies to S.sanguis cells, even though the same antibodies were dramatically affected by exposure to SDS at > 0.2% w/v.

Polyclonal anti-S.sanguis antibodies tested behaved similarly, although greater resistance to the chaotropic effects of SDS was observed as compared with the monoclonals.

Polyclonal anti-S.sanguis:

15

20

25

Detergent Concentration % (w/v)	O.D. 410 nm		
	Cremophor	Synperonic	SDS
0	1.593	1.601	1.743
0.02	1.575	1.627	1.767
0.05	1.545	1.667	1.772
0.1	1.532	1.668	1.442
0.2	1.614	1.803	1.16
0.5	1.617	1.692	1.159
1	1.496	1.531	0.882
2	1.513	1.724	1.013
5	1.4	1.537	0.687
10	1.45	1.555	0.626

30

Monoclonal anti-S.sanguis (IgM)

	Detergent Concentration % (w/v)	O.D. 410 nm		
		Cremophor	Synperonic	SDS
5	0	1.033	1.085	1.130
	0.02	1.004	1.171	1.022
	0.05	0.975	1.111	1.073
	0.1	0.978	1.110	0.862
	0.2	1.259	1.078	0.016
10	0.5	1.05	1.101	0.015
	1	1.074	1.197	0.015
	2	1.042	1.183	0.015
	5	1.036	1.197	0.015
15	10	1.083	1.138	0.015

EXAMPLE 5

20

The stability of anti-glucose oxidase antibody was tested in the following mouthwashes:

	<u>INGREDIENT</u>	<u>A</u> <u>% by weight</u>	<u>B</u> <u>% by weight</u>
25	Sorbitol	40.0	8.0
	Glycerol	-	4.0
	Ethanol	15.0	6.0
30	Glycine	1.0	-
	Synperonic F68	1.0	-
	Cremophor RH40	-	0.09
	Flavour oil	0.20	0.10
	Colour	0.03	0.25
35	NaF	0.02	0.05
	Saccharin	-	0.03
	Water	42.75	81.48
40	pH	6.0	6.5

A mouse monoclonal antibody against glucose oxidase was added to each mouthwash at a concentration of 60  $\mu$ g MAb/ml of mouthwash. Mouthwashes were stored in closed bottles for 1 year at 28°C.

5

### Experimental

Immunoreactivity of whole antibody against glucose oxidase was measured by enzyme linked immunosorbent assay (ELISA) in which glucose oxidase was immobilized on the surface of a nylon peg. The pegs were exposed sequentially to test paste samples containing anti-glucose oxidase antibody, anti-mouse alkaline phosphatase enzyme immuno-conjugate, and finally to enzyme substrate, para-nitrophenylphosphate. The generation of yellow product was measured by spectrophotometry (O.D. 405 nm).

Storage stability of anti-GOx in mouthwashes:

Time	Residual immunoreactivity	
	Mouthwash A	Mouthwash B
1 day	100 %	111 %
7 days	90 %	150 %
28 days	64 %	64 %
140 days	45 %	56 %
296 days	3 %	22 %

25

For comparison the same mouse monoclonal antibody against glucose oxidase (anti-GOx) was stored in phosphate buffered saline (PBS) pH 7.2 + 0.2 g/l sodium azide. The composition of PBS: 8.5 g/l NaCl + 1.07 g/l Na<sub>2</sub>HPO<sub>4</sub> (anhydrous) + 0.39 g/l NaH<sub>2</sub>PO<sub>4</sub>.2H<sub>2</sub>O. The solution was filter sterilised through a 0.22  $\mu$ m Millipore filter prior to storage. The anti-GOx was added at 60  $\mu$ g/ml. The solution was stored at 28°C. The residual immunoreactivity was measured with time.

30

35



Storage of anti-GOx in buffer:

5	Time	Residual immunoreactivity
	1 day	73 %
	7 days	100 %
	56 days	56 %
	84 days	56 %
	365 days	1 %

10

#### Example 6

Surfactant solutions were prepared in PBS:

- 15
1. Control (PBS only)
  2. 2 % SLS (Empicol LZPV/C)
  3. 2 % Cremophor RH40
  4. 2 % Synperonic PE/F68

20 All solutions were then heat sterilised. The Fv fragment of monoclonal antibody against lysozyme was added to each solution at a concentration of 10 µg Fv/ml. Solutions were stored in closed bottles at 28°C. The residual immunoreactivity was measured with time using the method

25 given in Example 3.

Storage stability of antibody fragment Fv-lys:

30	Time	Residual immunoreactivity			
		Control	SLS	Cremophor	Synperonic PE/F68
	1 day	100 %	0 %	75 %	82 %
	140 days	55 %	0 %	20 %	26 %
	274 days	97 %	0 %	40 %	55 %

C L A I M S

1. An oral composition comprising an antibody and a surfactant, characterised in that the surfactant is or comprises a nonionic surfactant.
2. A composition according to claim 1, characterised in that the nonionic surfactant is or comprises an ethylene oxide/propylene oxide block copolymer of the general formula  $H-(O-CH_2CH_2)_a-(O-CH-(CH_3)CH_2)_b-(O-CH_2CH_2)_a-OH$  in which a and b are integers greater than 0, said copolymer having an average molecular weight of between 4,000 and 15,000 and having an HLB-value between 27 and 30.5 and comprising about 80 % by weight of ethylene oxide in the molecule.
3. A composition according to claim 1, characterised in that the nonionic surfactant is or comprises a hydrogenated castor oil, condensed with 40-60 moles of ethylene oxide.
4. A composition according to claims 1-3, characterised in that the antibody is an antibody against S.sanguis or against glucose oxidase or against horse radish peroxidase.
5. A composition according to claims 1-4, characterised in that the oral care composition is a toothpaste or a mouthwash.
6. Use of a nonionic surfactant as stabilizing agent in antibody-containing oral care compositions.

FIG. 1/4

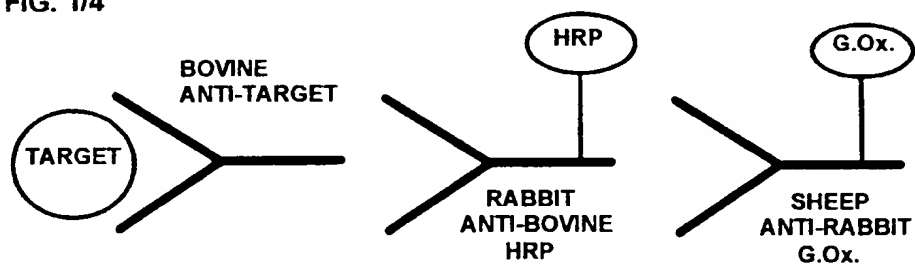
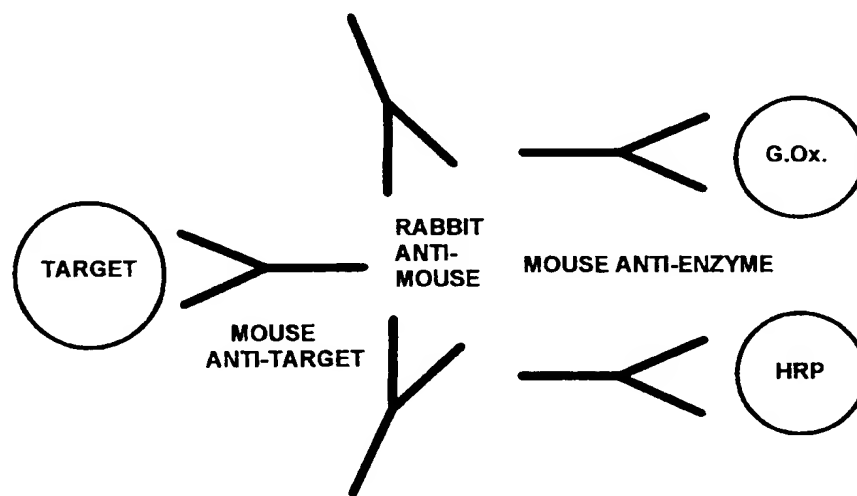


FIG. 2/4

**DOUBLE ENZYME SELF ASSEMBLING COMPLEX (DESC)**

2/2

FIG. 3/4

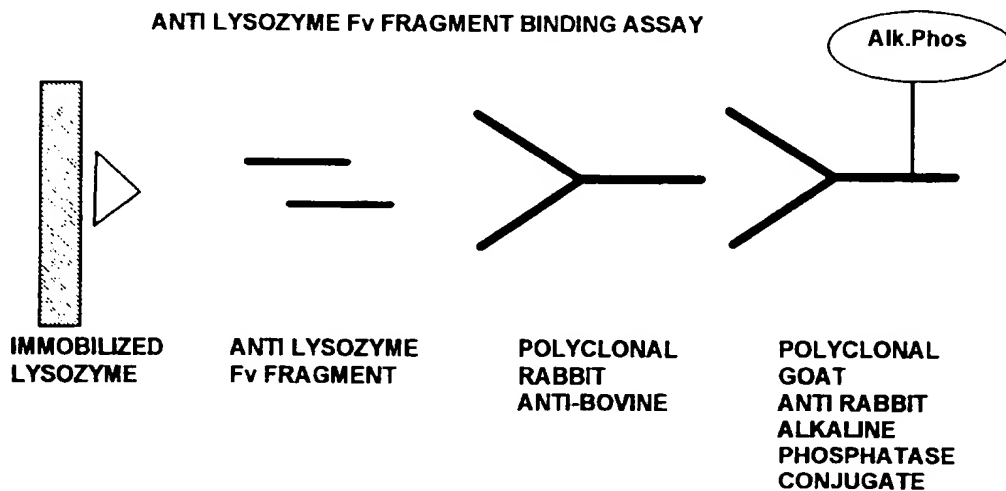
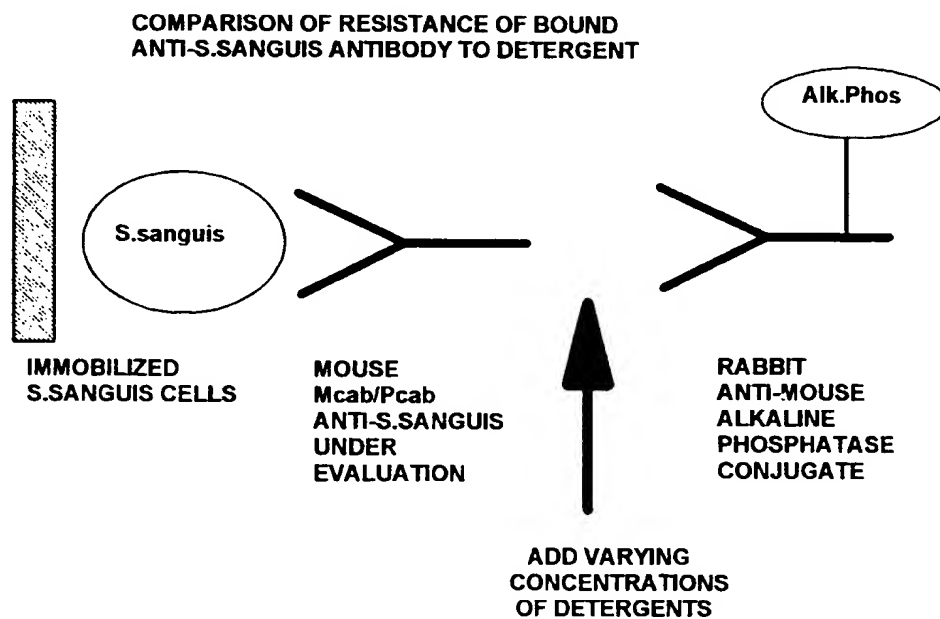


FIG. 4/4



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/02132

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K7/16 A61K47/10 A61K47/42

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 8706, Derwent Publications Ltd., London, GB; AN 87-040921 (06) see abstract & JP,A,62 000 417 (LION CORP.) 6 January 1987 ---	1,2,5,6
Y	PATENT ABSTRACTS OF JAPAN vol. 010, no. 296 (C-377) 8 October 1986 & JP,A,61 112 028 (LION CORP.) 30 May 1986 see abstract ---	1-6
Y	GB,A,2 176 400 (LION CORP.) 31 December 1986 see claims see examples see page 3, line 43 - line 59 -----	1-6

☐ Further documents are listed in the continuation of box C.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP-A-62000417	06-01-87	NONE	
GB-A-2176400	31-12-86	JP-A- 61289024	19-12-86
		DE-A- 3619904	18-12-86
		US-A- 4911918	27-03-90